UNIQUE SYNTHETIC TRANSFORMATIONS PROMOTED BY LIGHT

THORSTEN BACH

Department Chemie and Catalysis Research Center (CRC), School of Natural Sciences, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany

Sustainable Synthesis and the Role of Light

The absorption of a photon by a molecule represents an enormous uptake of energy. One mole of photons (i.e. 6.022×10^{23}) with a wavelength (λ) of 400 nm correlates to an energy of 300 kJ. If the wavelength is shorter, e.g. $\lambda = 300$ nm, the energy uptake is even higher, in this case 400 kJ mol^{-1}. As a result, excited molecules can perform chemistry that requires high activation barriers or is completely impossible in the ground state. Although Ciamician already recognized [1] the sustainability of sunlight-mediated reactions more than hundred years ago, now is the time to move forward and to devise photochemical reactions that provide solutions for key challenges in the era of climate change. In this context, I admire the formidable input delivered by many researchers worldwide on key topics in photocatalysis, such as carbon dioxide reduction [2], hydrogen generation from water [3], nitrogen fixation [4], or solar cell development [5], to name a few.

My own interest in the role of light touches equally fundamental questions, yet it pertains to structure and selectivity parameters associated with photochemical reactions. Photochemistry can overcome the boundaries of ground state reactions, because the intrinsic energy uptake provides a handle to access products that are higher in energy than the starting materials. It allows to reach reaction pathways that are thermally inaccessible. I find three aspects particularly fascinating: (a) Arenes, most notably benzene rings, are extremely stable, and their aromaticity can only be overcome by strong reductants or oxidants. On the other hand, given their abundance and ready availability, arenes represent excellent building blocks for the creation of defined three-dimensional skeletons, and photocatalysis offers the perfect tools to do so. Whether for skeletons of pharmaceutical relevance with the "escape from flatland" as a novel paradigm in medicinal chemistry [6] or for the synthesis of natural products, creative methodology is required to allow for the defined conversion of benzene rings into complex, alicyclic products. (b) Excitation takes a substrate molecule to electronic states that are several hundreds of kJ mol^{-1} above the ground state. The substrates typically pass through easily accessible reaction channels to intriguing products with a cyclobutane arguably presenting the signature structure and the [2+2] photocycloaddition representing the

hallmark reaction of photochemistry [7]. Due to the low activation barriers of photochemical reactions it has long appeared impossible to control the three-dimensional structure of products, i.e. their absolute configuration, in photochemical reactions. (c) In the latter context, photochemistry offers an alternative approach to enantiomerically pure compounds starting from their racemates. The entropic penalty of this process, which is impossible to accommodate in the ground state, is compensated by light energy. Among other contra-thermodynamic processes [8], photochemical deracemization appears to have the widest impact due to the ever-increasing demand for enantiomerically pure compounds. With racemic product mixtures available at low cost, their comprehensive transformation into single enantiomers represents a highly sustainable method to be performed with solar irradiation.

My recent research contributions

Work in my group focusses on the development and application of new catalytic methods for organic synthesis. We have devised enantioselective methods for C–H activation [9,10] and we have developed new reactions for the total synthesis of biologically active natural products [11,12]. Most of my research output in recent years, however, has been devoted to the exploration of unchartered territory in photochemistry and photocatalysis. A few examples are given below and are illustrated by Figures 1 and 2.

My interest in arene photochemistry has led to one-step protocols in which flat, readily available ingredients, such as indanone **1**, are converted in a single photochemical operation into complex three-dimensional structures like pentacyclic product **2**. Cascade reactions of this type involving the uptake of multiple photons have been successfully implemented in the first total synthesis of the sesquiterpene natural products atlanticone C and agarozizanol B (**4**) [13,14]. In the latter synthesis, the easily available compound **3** served as the precursor to prepare the desired product in a concise fashion with the photocascade reaction as a powerful overture.

My group has been on the forefront of the quest for enantioselectivity in photochemical reactions. As early as 2005, a key publication [15] showed that this challenge, previously considered unsurmountable, can indeed be met, and we have designed chiral energy transfer photocatalysts that operate by recruiting substrates *via* hydrogen bonding interactions [16,17]. The compounds combine high catalytic activity with a broad scope for applications in [2+2] photocycloaddition chemistry and beyond. An alternative approach towards enantioselective photocatalysis rests on the use of chiral Lewis acids for the activation of chromophores towards a selective excitation. Many carbonyl groups that are conjugated to double bonds display an absorption shift to longer wavelength (bathochromic) when coordinated to a Lewis acid, and the complex can be selectively excited by judicious choice of the excitation source (chromophore activation). The approach paved the way for the first enantioselective [2+2] photocycloaddition of enones [18,19] employing chiral oxazaborolidines as Lewis acids. Catalysts **6** have also been used for the enantioselective *ortho* photocycloaddition on arenes (**5** → **7**) [20] and for the

enantioselective oxadi-π-methane rearrangement of dienones (**8** → **9**) [21]. The enantiomeric excess (*ee*) is a measure for the degree of enantioselectivity achieved in asymmetric catalysis, and relates to the excess of one enantiomer relative to its mirror image. A ratio of 97/3, for example, means that the excess is 94% *ee*.

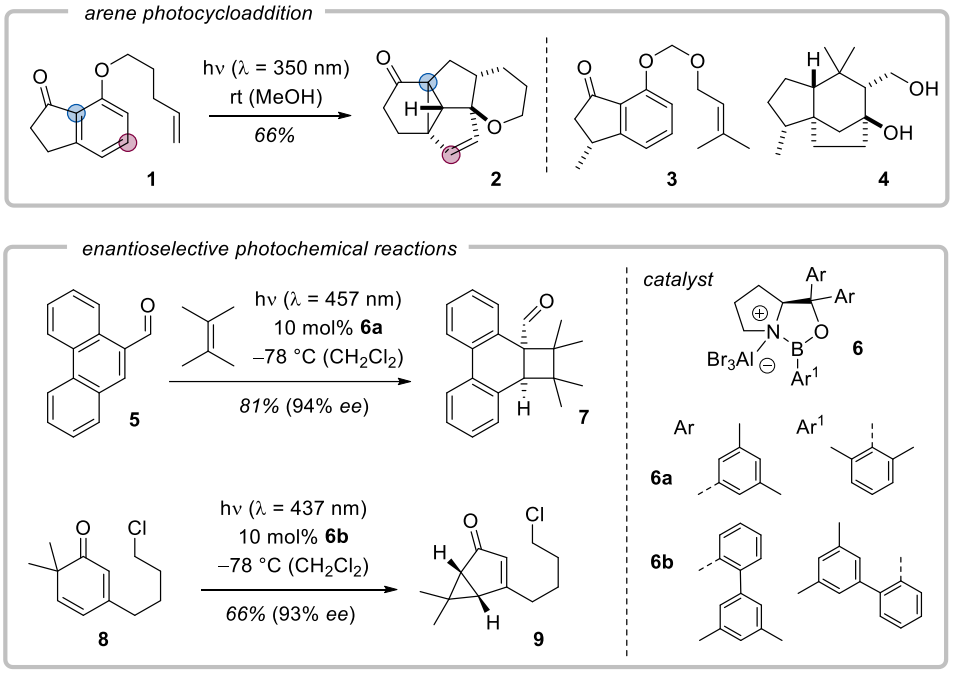

Fig. 1. Arene photocycloaddition chemistry enables the formation of complex products such as **2** from simple achiral substrates such as **1**. The marked atoms help to understand the topology of the reaction. By employing compound **3** as the starting material the natural product agarozizanol B (**4**) became available in a short route (top). $AlBr_3$-activated oxazaborolidines **6** serve as powerful catalysts for several enantioselective photochemical reactions, e.g. an *ortho* photocycloaddition (**5** → **7**) or an oxadi-π-methane rearrangement (**8** → **9**) (bottom).

Given the great demand for enantiomerically pure compounds, photochemical deracemization represents a perfect transformation to access them directly from their respective racemates. My group reported the first example for a reaction of this type in 2018 [22], and the field has been growing rapidly ever since [23,24]. Conceptually, we have attempted to work with a single photocatalyst that recognizes the substrate by hydrogen bonding interactions. Thioxanthone **11**, for example, can successfully distinguish between allene enantiomer **10** and its mirror image *ent*-**10**. Upon excitation, it promotes almost exclusively the latter compound into an achiral triplet state from which relaxation leads statistically to **10** and *ent*-**10**. After several catalytic cycles, the photostationary state is shifted towards the product which was eventually isolated quantitatively in 95% *ee*.

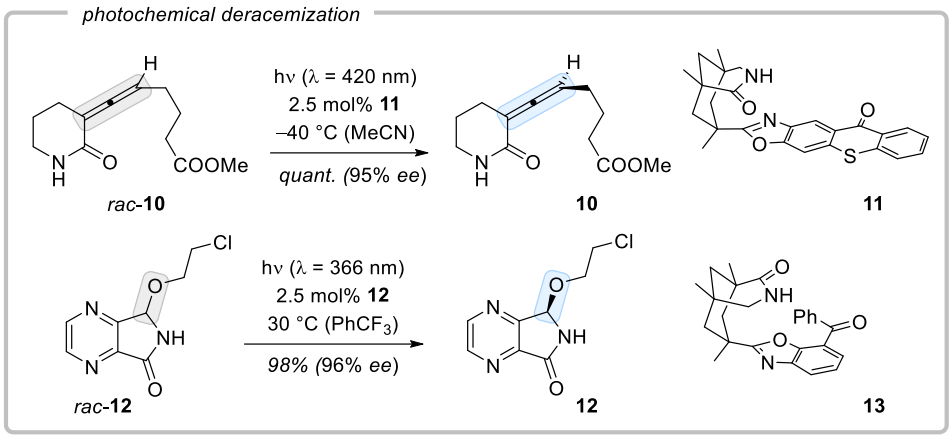

Fig. 2. Photochemical deracemization reactions: Catalyst **11** allows for the conversion of allene *rac*-**10** into a single enantiomer by selective energy transfer. A reversible hydrogen atom transfer to and from benzophenone **13** is key to the success in the deracemization of 4,7-diaza-1-isoindolone *rac*-**12**.

Catalyst **13** operates by a reversible hydrogen atom abstraction which means that it picks selectively a hydrogen atom from one enantiomer of racemic 4,7-diaza-1-isoindolone *rac*-**12**. Since the return hydrogen atom transfer is unselective, a similar scenario as described above applies and the photostationary state is shifted towards a single enantiomer [25]. Many substrate classes to which photochemical deracemization can be applied are active pharmaceutical ingredients or immediate precursors thereof.

Outlook to future developments

My specific vision for the photochemistry we have been doing within the last ten years relates to its application on larger scale, ideally driven by sunlight. Further improvement of the quantum efficiency might be required for some processes, but I believe the issue can be solved. In particular, the deracemization chemistry should be appealing to anyone who requires access to a given compound in enantiomerically pure form. Since deracemization allows in principle for editing every stereogenic element within a molecule in successive order, an ideal scenario would be to take a stereochemically undefined molecule, i.e. a mixture of stereoisomers, and to edit its stereochemistry by selecting a suitable photocatalyst (stereochemical editing). Beyond my current expertise, I expect photochemistry to have a translational impact on the way we use solar energy for the production of chemicals in all areas of everyday life, be it in bulk or on smaller scale. The key issue will be to find robust processes which allow for harvesting solar photons efficiently and which convert photonic energy into reduction equivalents.

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